III. REMARKS

This paper is filed in response to the Office Action dated June 10, 2009, in connection with the above-identified patent application.

Claims 1-3 and 8-26 are pending. Claims 2, 3, and 9-25 have been withdrawn.

By this Amendment, claims 1-3 are canceled, and claims 8 and 26 are amended. Support for the amendment can be found in the specification and claims as originally filed. For example, Applicants have amended claim 8 to be limited to a single compound, and claim 26 to properly depend from a pending claim. Applicants submit that the amendments and cancellation of claims are made without prejudice or disclaimer. Applicants submit that no new matter has been added and respectfully request reconsideration and withdrawal of the pending rejections.

Supplemental Information Disclosure Statement

The Examiner indicated that a copy of one of the references (Clark et al., *Br. J. Pharmacol.,* 2000, 129-98P) cited in the Information Disclosure Statement filed on March 10, 2009, was not submitted. Applicants are concurrently filing a Supplemental Disclosure Statement submitting this reference.

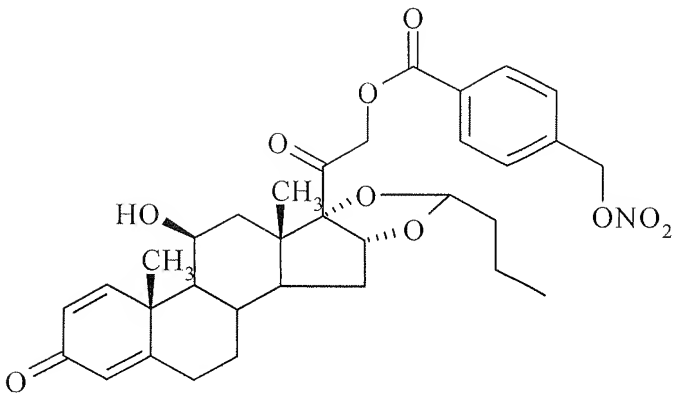
Title of the Invention

The Examiner objected to the title of the invention for not being descriptive. Applicants have amended the title of the invention to "Nitrooxyderivatives of Steroidal Compounds." In light of this amendment, Applicants respectfully request reconsideration and withdrawal of the objection to the title.

Double Patenting

Claims 1, 8 and 26 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims of U.S. Patent No. 7,056,905 (hereinafter "the '905 patent") and U.S. Patent No. 6,610,676 (hereinafter "the '676 patent"). Applicants traverse the rejection.

Claim 1 has been canceled, and claim 8 has been amended to recite only the following compound: budesonide 21-(4'-nitrooxymethyl)benzoate:



Applicants submit that present claim 8 is patentably distinct from the claims of the '905 patent and the '676 patent. Applicants submit that, unlike the precursor (budesonide), the claimed budesonide derivative can be used in respiratory pathologies characterized by broncho-obstructive events. Applicants submit that this is unexpected, as budesonide is substantially ineffective for use in these respiratory pathologies. The present specification notes that precursor compounds such as budesonide "must be associated with broncho-dilators as beta-agonists such [as] for example salbutamol" (page 23, lines 24-31). The present specification shows that the claimed compound of budesonide 21-(4'-nitrooxymethyl)benzoate inhibits bronchoconstriction caused by histamine. In contrast, bronchoconstriction is worsened with use of the budesonide. See Example F3 on pages 41-42 of the specification.

Applicants respectfully submit that the '905 patent and '676 patent do not teach or suggest that the claimed compound can result in these unexpected benefits, and therefore the claims of the present application are not an obvious variation of the claims of the '905 patent and the '676 patent. For instance, the examples of the '905 patent and '676 patent discuss antiarthritic activity (Example 2B), gastric tolerability (Example 2C), bone toxicity (Example 2E), cardiovascular safety (Example 2E), and angiostatic activity (Example 2D). The examples do not discuss the effect on respiratory pathologies characterized by broncho-obstructive events.

Applicants additionally note that the presently claimed compound of budesonide 21-(4'-nitrooxymethyl)benzoate has been shown to have additional unexpected results. Applicants enclose a copy of the following reference: Boulet et al. "Safety, pharmacodynamics and pharmacokinetics of TPI 1020 in smokers with asthma."

Respiratory Medicine, (2009) 103, 1159-1166 (hereinafter "Boulet"). Applicants submit that Boulet shows that budesonide 21-(4'-nitrooxymethyl)benzoate, which is also called TPI 1020, has unexpected results in human smokers with asthma. Boulet shows that inhaled budesonide 21-(4'-nitrooxymethyl)benzoate had similar improvement compared to inhaled equimolar doses of budesonide relating to clinical parameters, such as peak expiratory flow, rescue free days, and use of rescue medication (see Table IIa) and inflammatory parameters such as exhaled nitric oxide, sputum, and blood eosinophils (see Table IIb). However, Boulet also showed that, unexpectedly, budesonide 21-(4'-nitrooxymethyl)benzoate showed an additional more potent anti-inflammatory effect in significantly decreasing serum CRP at 14 days and significantly decreasing blood lymphocytes at 21 days. Applicants submit that these results were obtained with a better pharmacokinetic profile of serum budesonide (see Figure 5). In addition, the compounds had no effects on 24 hour urinary cortisol, while, as expected, budesonide significantly decreased 24 hour urinary cortisol (see Figure 2). Applicants submit that this means that the claimed compound has minor systemic absorption and therefore results in less side effects.

In summary, Applicants submit that the present claims are not an obvious variation of the claims of the '905 patent and the '676 patent. Applicants submit that the presently claimed invention is patentably distinct from the claimed compounds of the '905 patent and '676 patent. Applicants respectfully submit that the double patenting rejection of claims 1, 8 and 26 over the claims of the '905 patent and '676 patent is improper and request reconsideration and withdrawal of the rejection.

Rejection under 35 U.S.C. § 103(a)

Claims 1, 8, and 26 are rejected under 35 U.S.C. §103(a) as being unpatentable over Del Soldato (WO 98/15568, hereinafter "Del Soldato"). Applicants traverse the rejection.

Claims 8 and 26 have been discussed above. Claim 1 has been canceled. Del Soldato is a PCT application which is related to both the '905 patent and the '676 patent, which have been discussed above, relating to the double patenting rejection.

As discussed above, Applicants submit that the presently claimed invention demonstrates unexpected results which are not taught or suggested by Del Soldato. For example, based on the teachings of Del Soldato and without the benefit of hindsight, one of ordinary skill in the art would not have understood that the claimed compound can be used in respiratory pathologies characterized by broncho-obstructive events. Further, one of ordinary skill in the art would not have understood that administration of the claimed compound can result in a more potent anti-inflammatory effect in significantly decreasing serum CRP at 14 days and significantly decreasing blood lymphocytes at 21 days in human smokers with asthma. Therefore, Applicants submit that the presently claimed invention is not obvious in light of the teachings of Del Soldato.

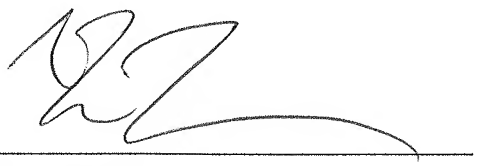
Applicants respectfully request reconsideration and withdrawal of the rejection of claims 1, 8, and 26 under 35 U.S.C. § 103(a) over Del Soldato.

IV. CONCLUSION

Applicants respectfully submit that this application is in condition for allowance and such action is earnestly solicited. If the Examiner believes that anything further is desirable in order to place this application in even better condition for allowance, the Examiner is invited to contact Applicants' undersigned representative at the telephone number listed below to schedule a personal or telephone interview to discuss any remaining issues.

In the event this response is not timely filed, the Applicants hereby petition for an appropriate extension of time. The fee for this extension, along with any other additional fees which may be required with respect to this response, may be charged to Deposit Account No. 01-2300, referencing Attorney Docket No. **026220-00048**.

Respectfully submitted,



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Enclosure: Boulet et al. "Safety, pharmacodynamics and pharmacokinetics of TPI 1020 in smokers with asthma." *Respiratory Medicine*, (2009) 103, 1159-1166